ROMA
21 novembre 2014

Per una corretta pratica clinica
della Malattia di Huntington

Il ruolo della diagnostica per immagini Nella comprensione della malattia di Huntington

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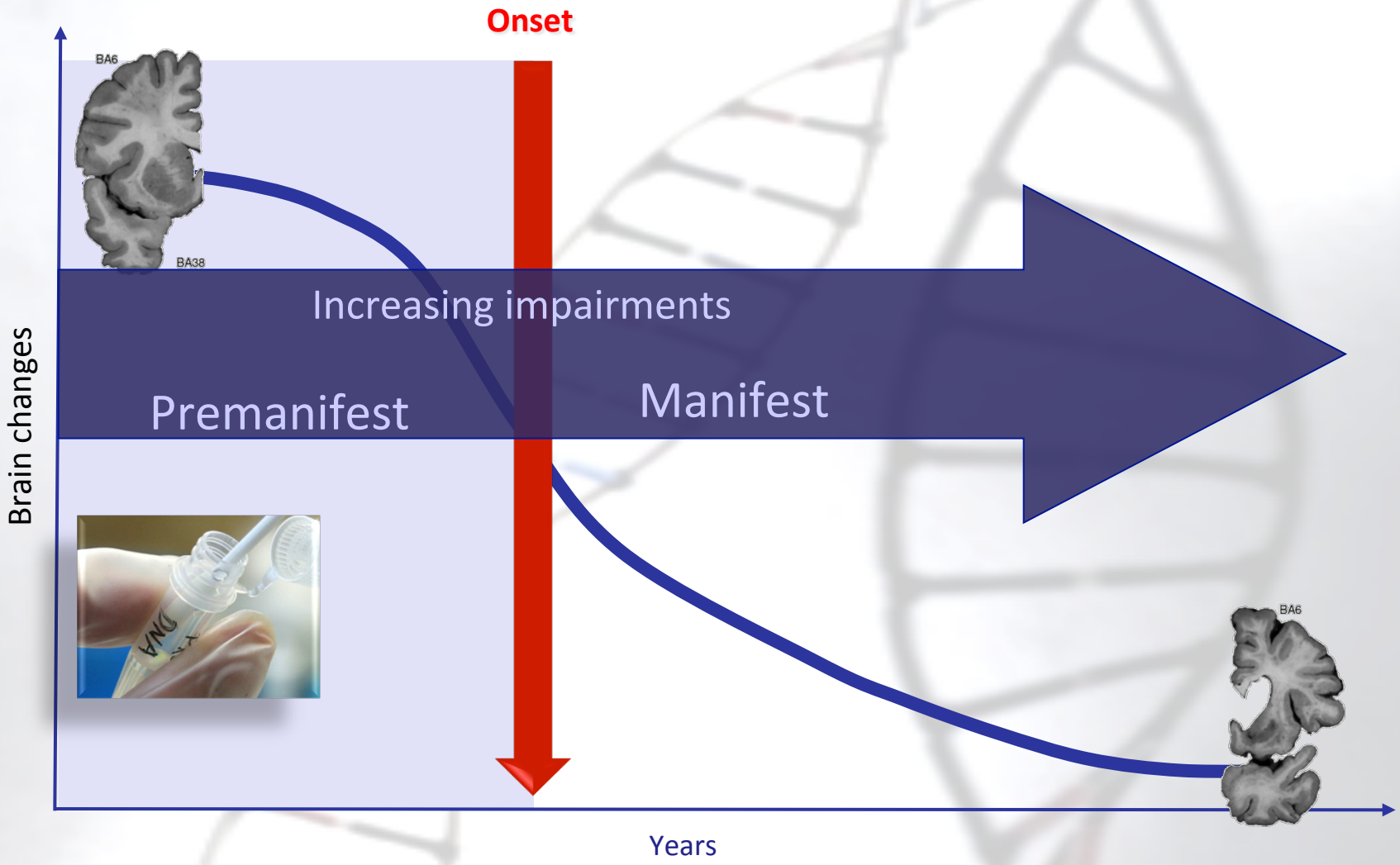
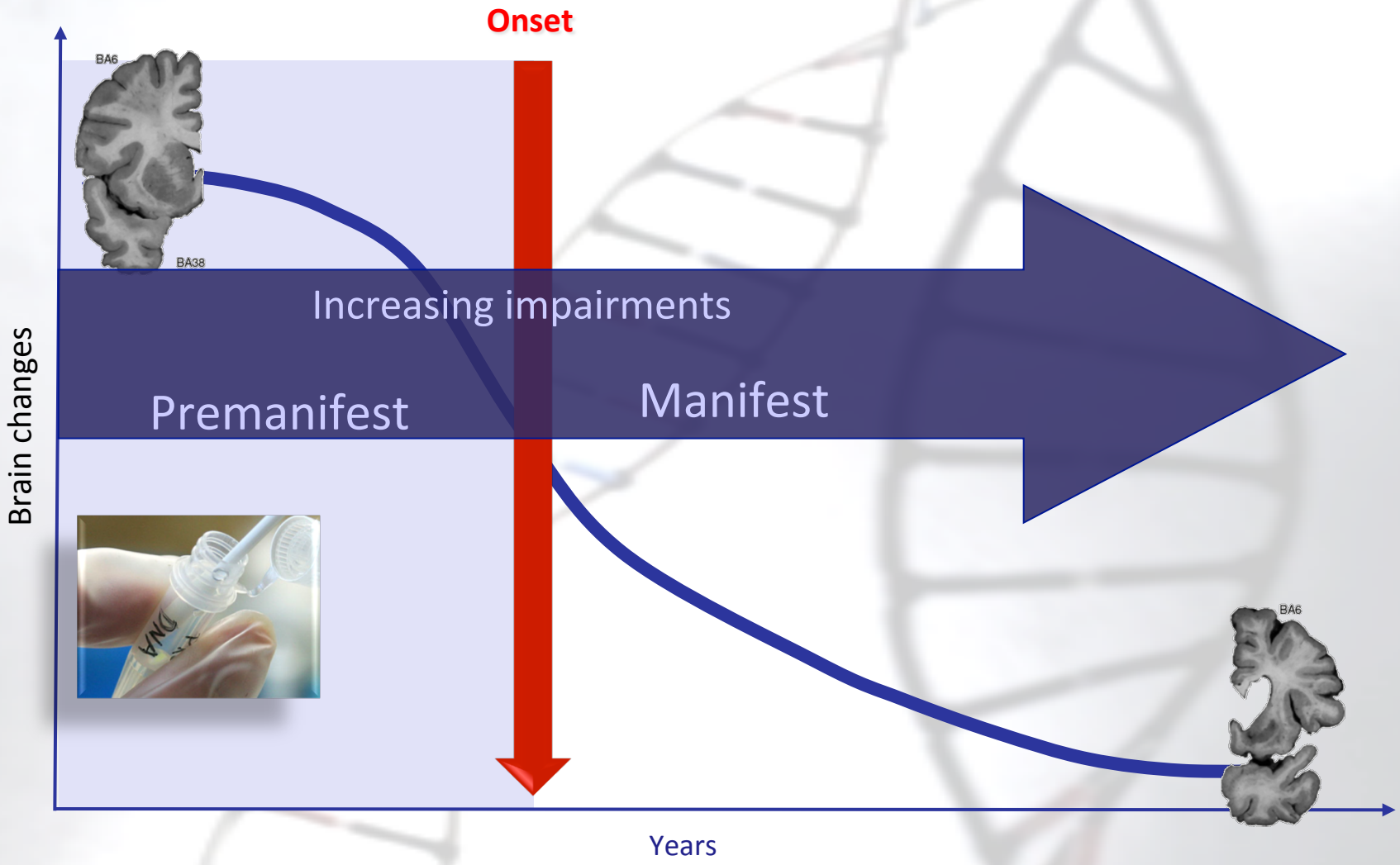
Dipartimento di Radiologia, IRCCS Fondazione S. Lucia

HD clinical and brain evolution



HD clinical and brain evolution

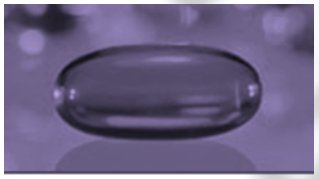


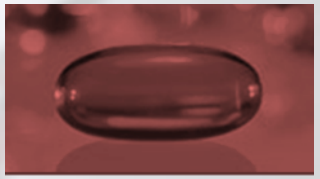
HD

1 – genetic test allows preclinical diagnosis
2 – starts many years before the symptoms
3 – induces progressive structural changes
4 – induces progressive functional changes

Disease-modifying therapeutics
to delay the onset and slow the progression

Model for other more commun
neurodegenerative diseases, AD, PD



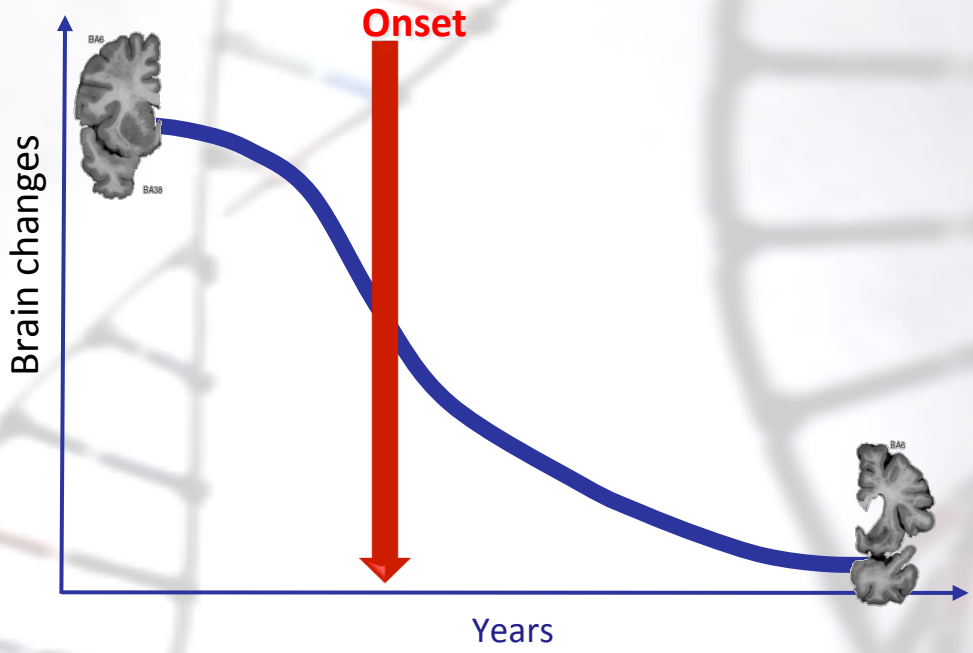


What is the role of neuroimaging in the Huntington disease?

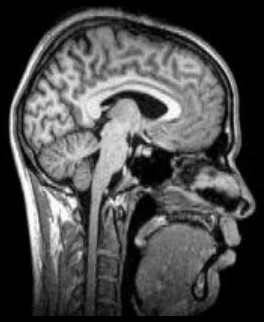
Is a neuroimaging a biological marker?

Definition: Indicator of normal and pathogenic biological process

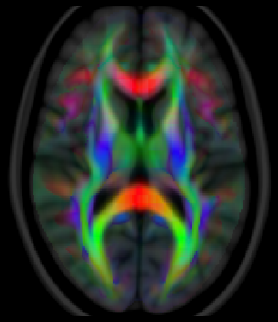
Criteria:
- Objectively measured
- Predicts clinical end point
- Associated with known disease mechanism and pathology
- Surrogate clinical end point
- Predicts responses to a therapeutic intervention



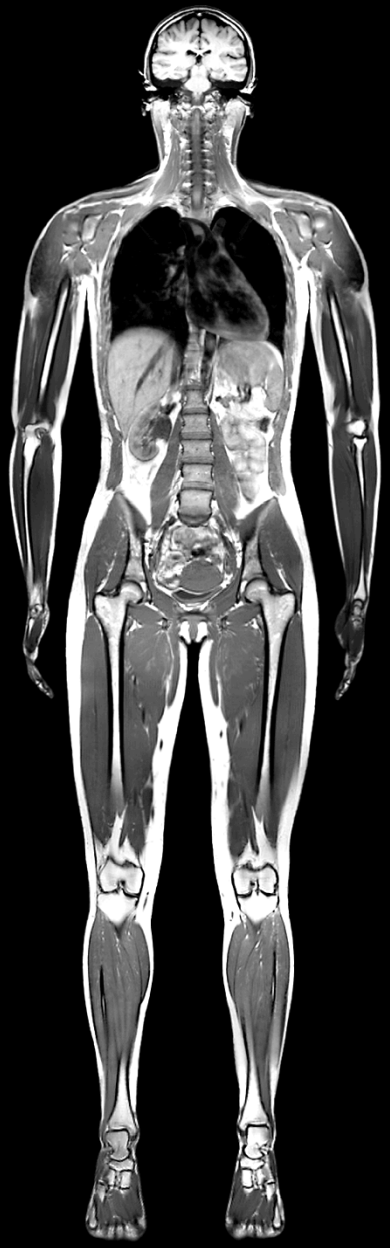
High field MRI 3T

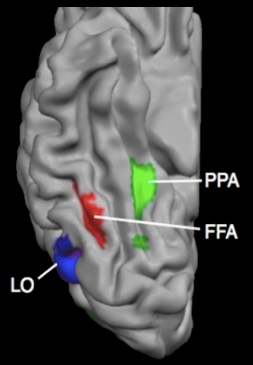


Macrostructure

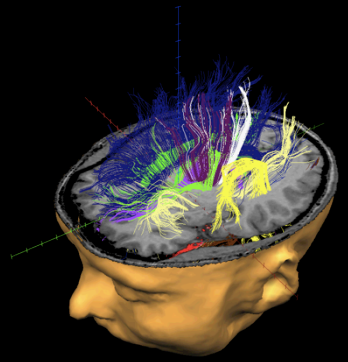


Microstructure

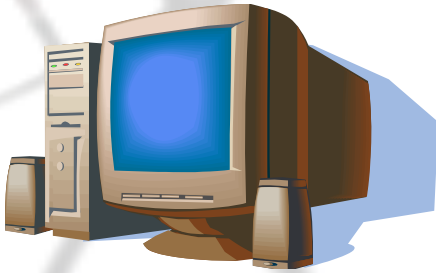




Function



Connectivity



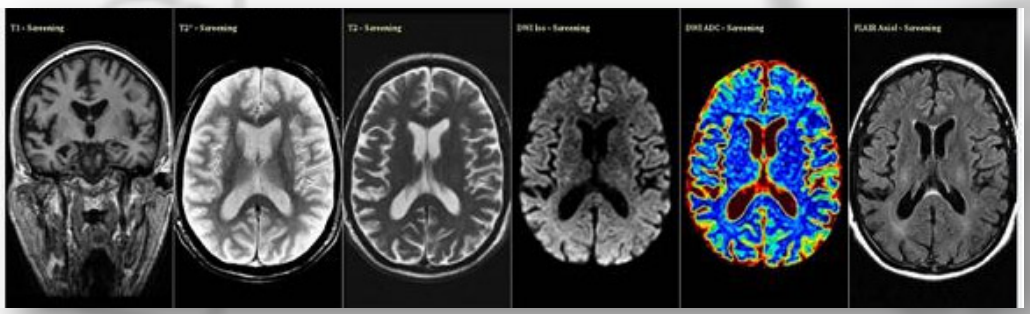
QUALITATIVE

Taking pictures; visualising
Focal defects (lesions), present or not
Description of the imaging features
Subjective; hard to reproduce
Dependent to radiologist experience
Conventional imaging techniques

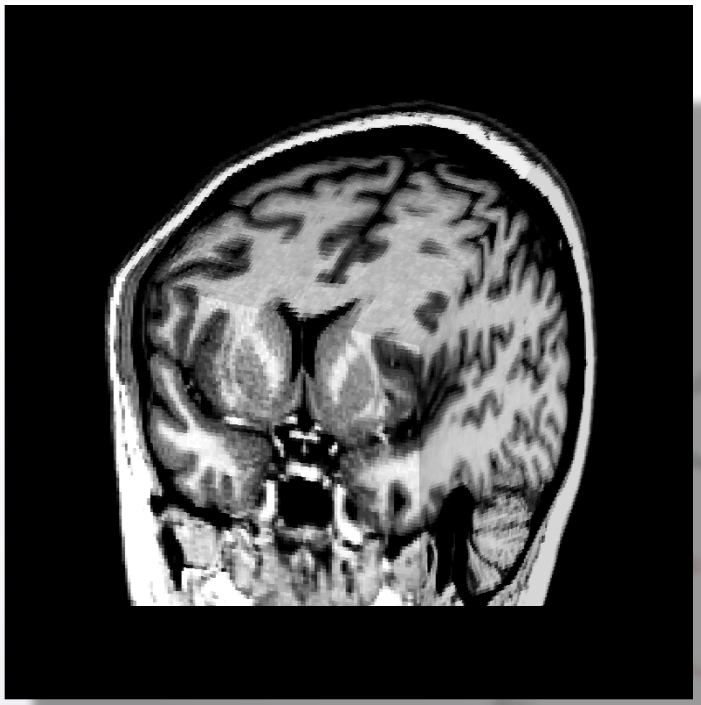
QUANTITATIVE

Allows measurement of subtle/invisible changes
Measurement of imaging parameters
Quantitation, diffuse or small
Objective, reproducible
Independent to radiologist experience
Advanced techniques

Individual profile



Multimodal MRI biomarkers



What can we measure?

T1
T2
T2* (Iron, mineralization)
Diffusion tensor: MD, FA
BOLD

Indirect measure of physical parameters which allow the macro-microscopic tissue structure and damage to be assessed

↓

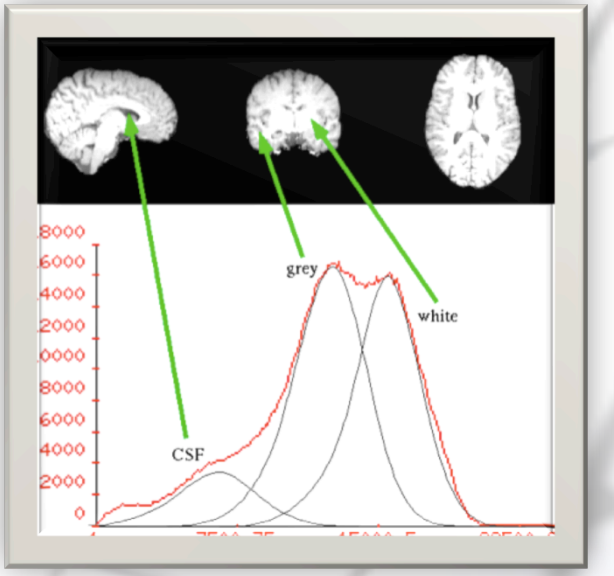
quantitative profile

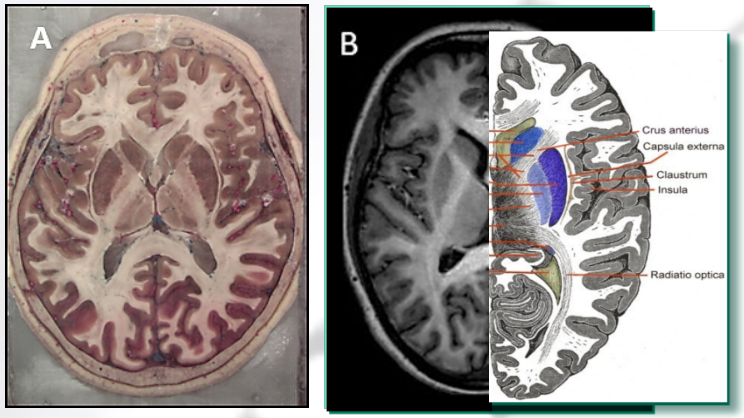
↓

biological marker

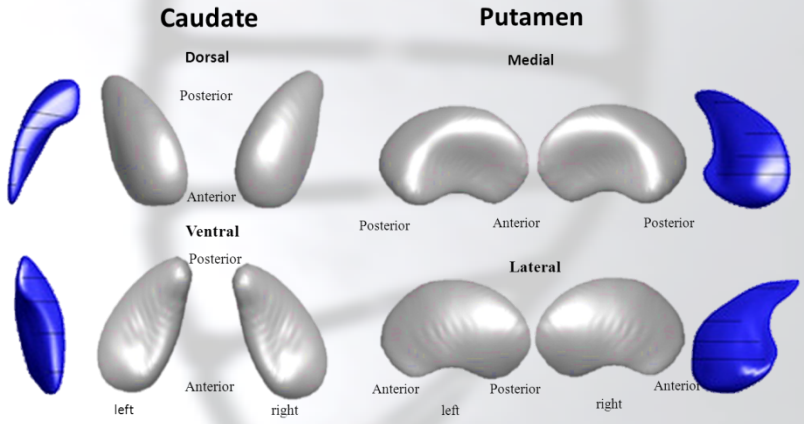
Macrostructural biomarker: T1

3 main tissue types in the brain: grey matter, white matter, CSF





anatomy



segmentation

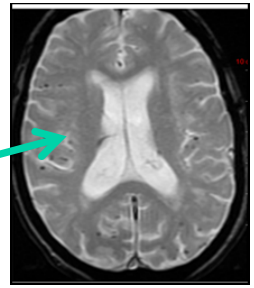
Microstructural biomarkers: T2*, MD, FA

Normal tissue

Pathological changes

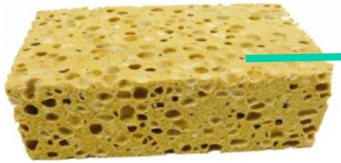
Increase iron deposition

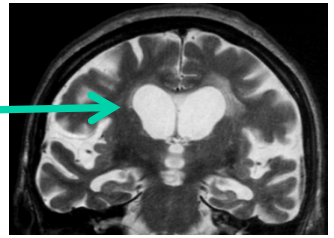
Relaxation time (T2*)



Tissue distruction

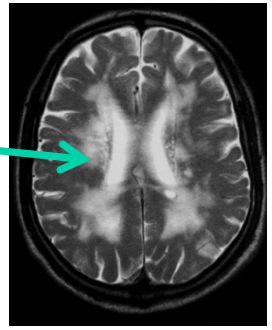
Mean diffusivity (MD)





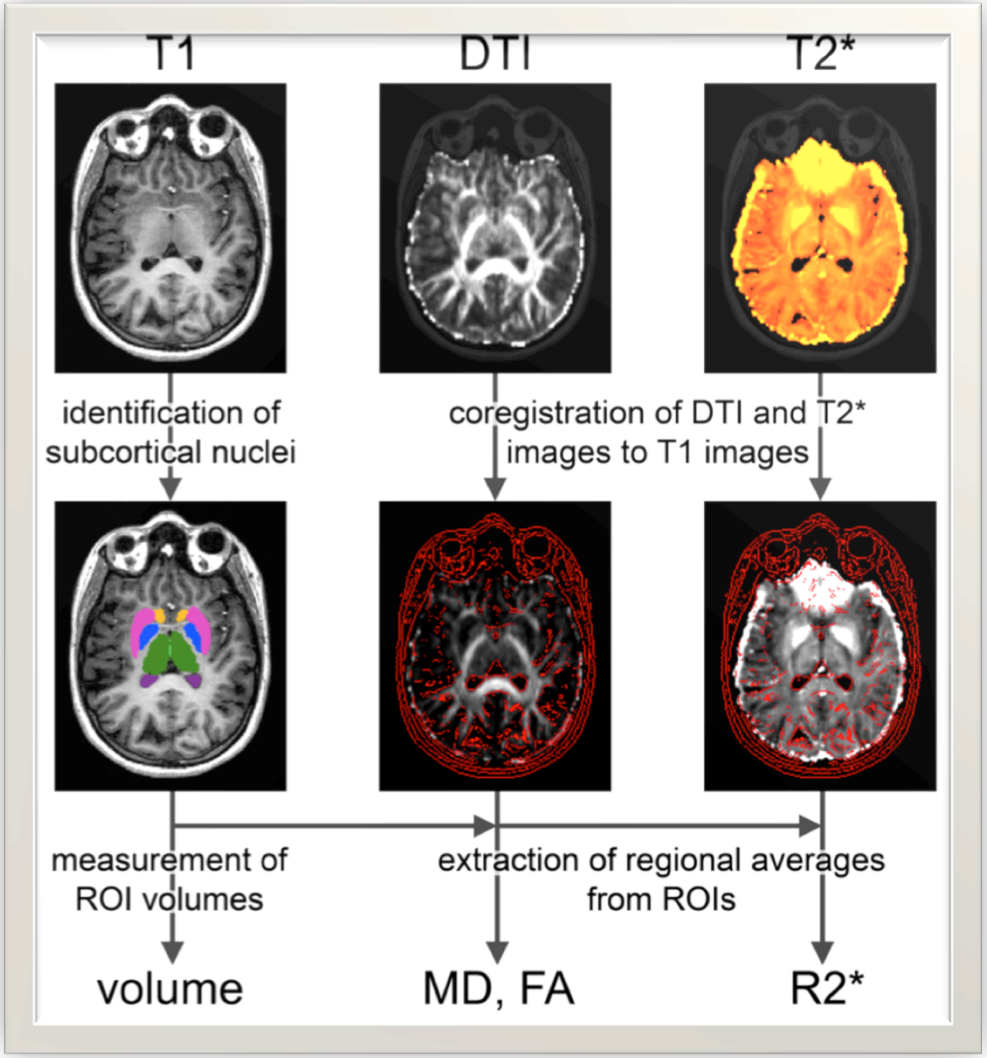
Abnormal fibers orientation

Fractional anisotropy (FA)



Characteristic profile of tissues

…To combine anatomy and microstructural markers



Workflow

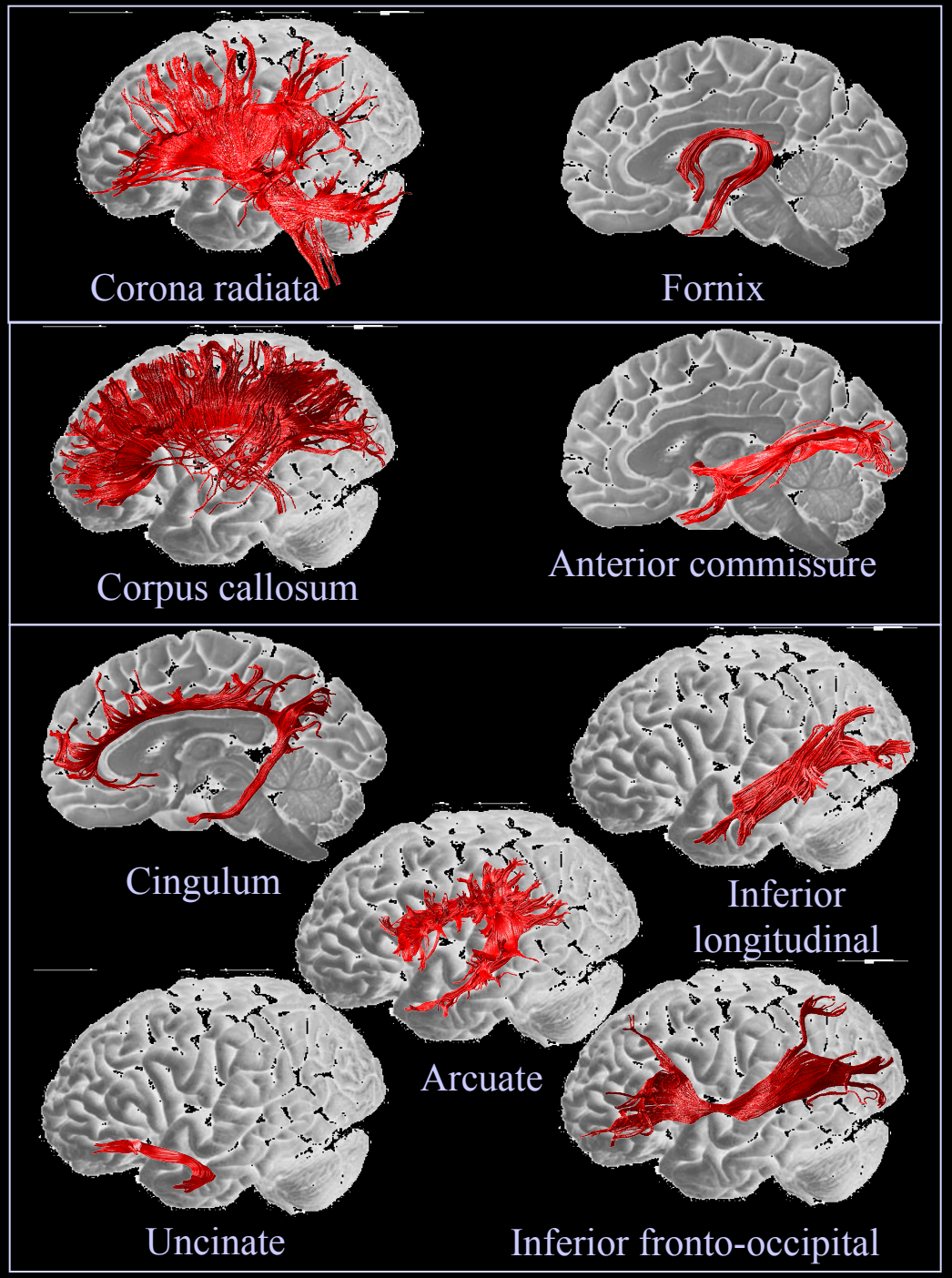
1. Automatic analysis
2. Coregistration different image modalities
3. Delineation anatomy, i.e. subcortical nuclei
4. Measurement of volume
5. Extraction of multiple biomarkers
6. Generation of normative ranges

Diffusion tractography

PROJECTION

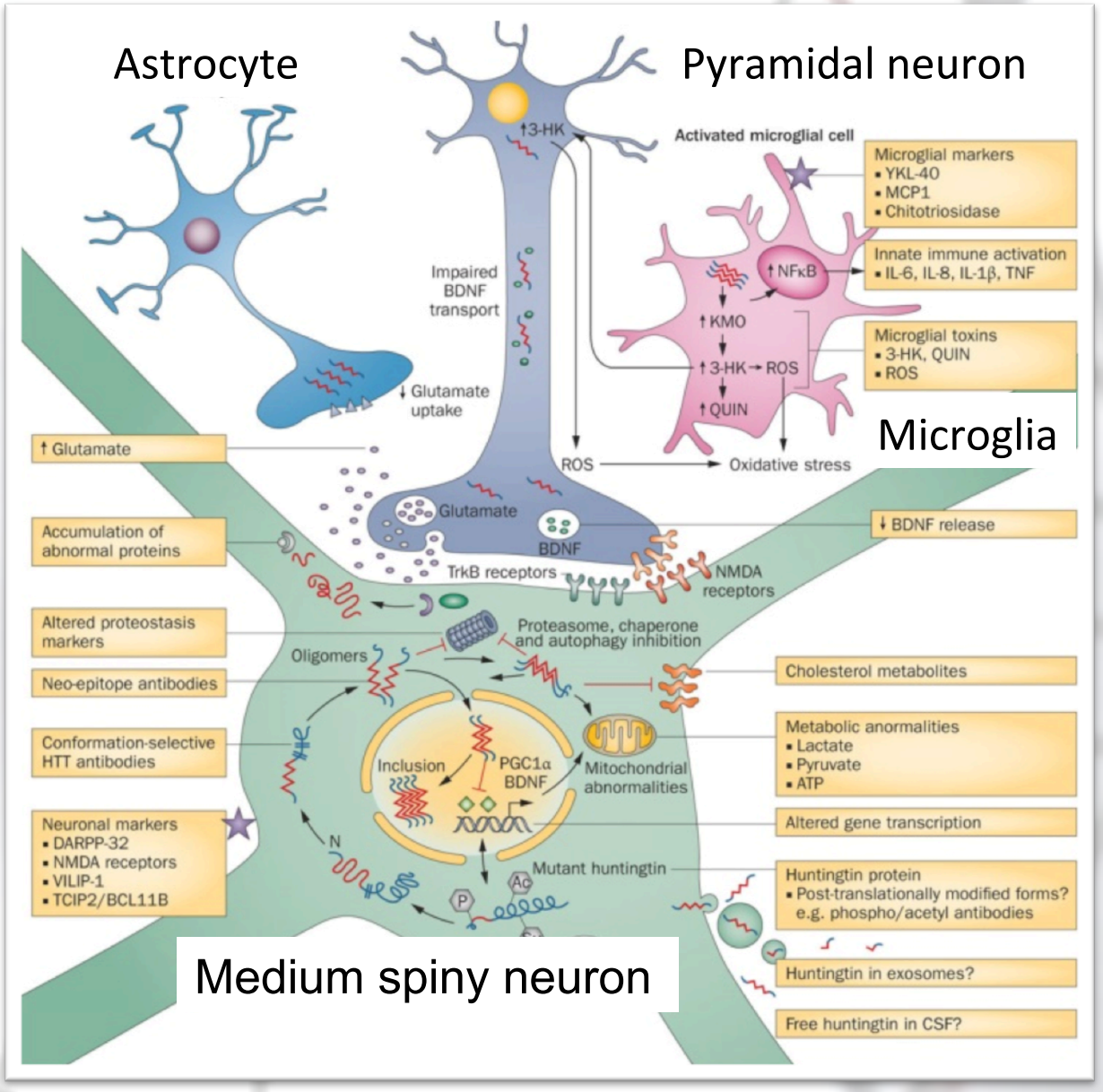
COMMISSURAL

ASSOCIATION



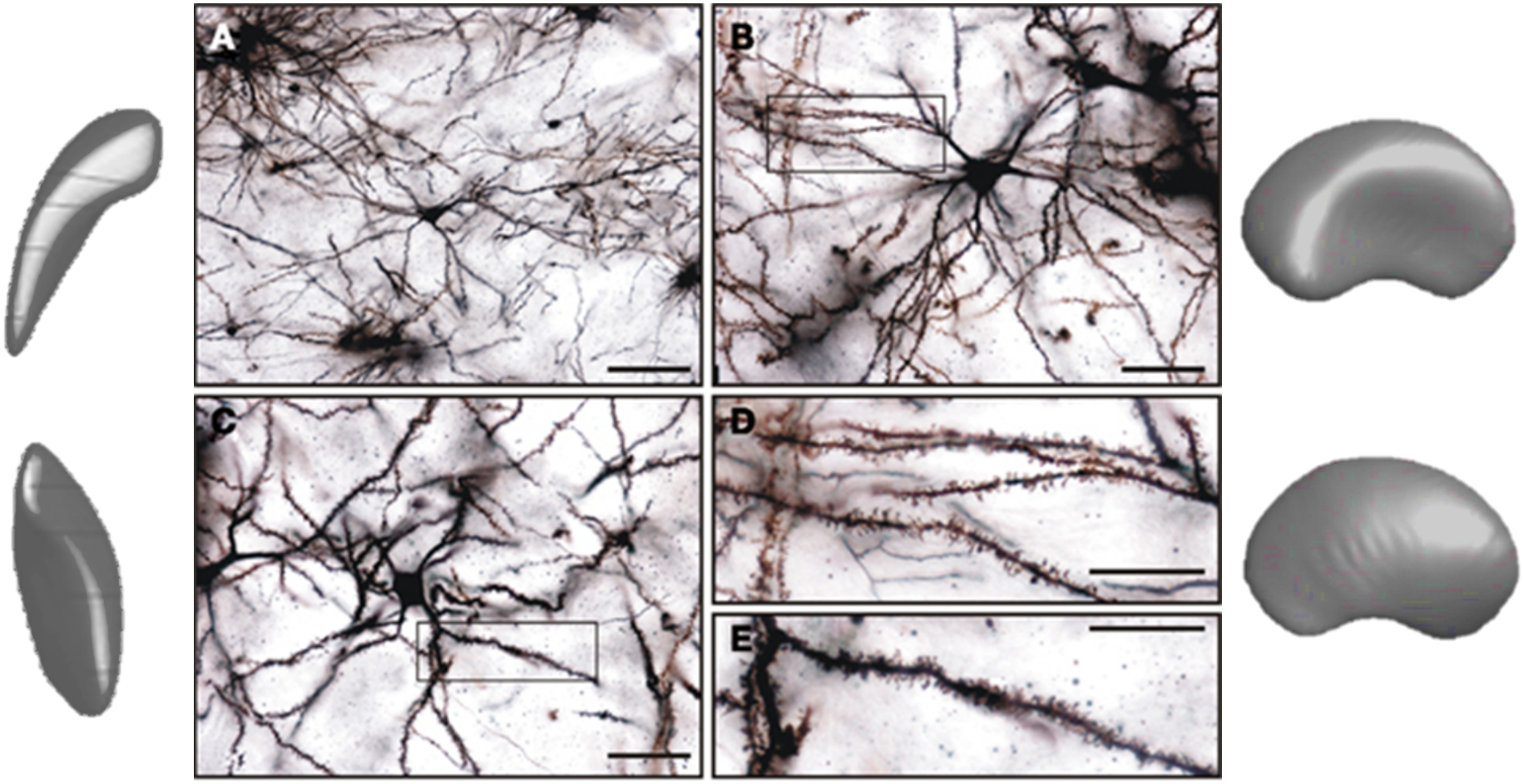
From HD physiopathology to imaging

HD pathogenesis: neuronal dysfuntion, neuronal death



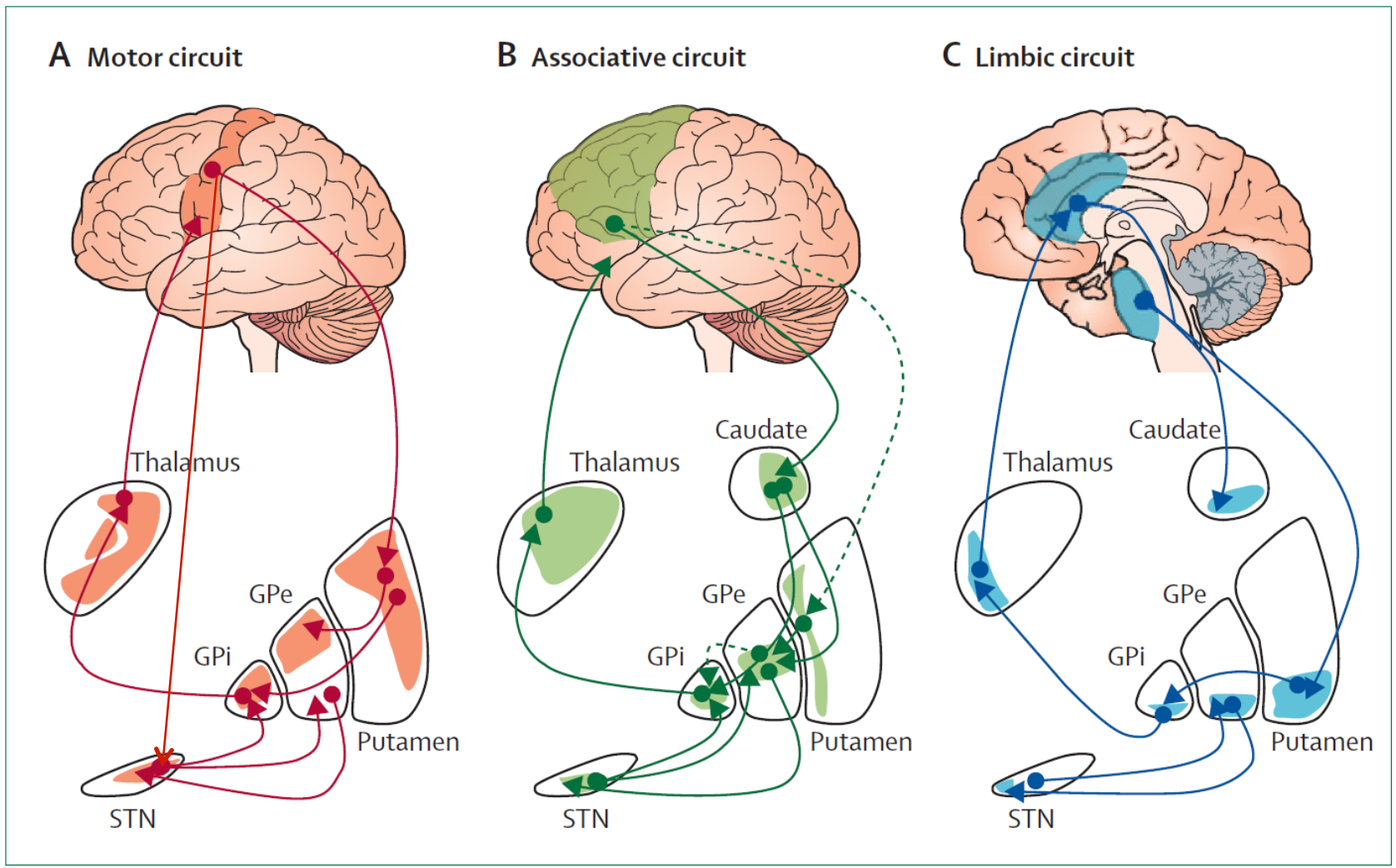
Ross et al, Nat Rev Neurol 2014

HD pathogenesis: striatal neurons dysfuntion and death



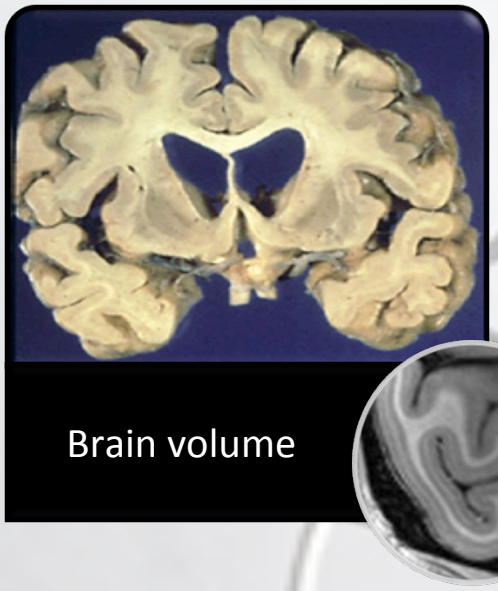
75% medium spiny neurons (GABAergic), project outside

Cortical projections to striatum

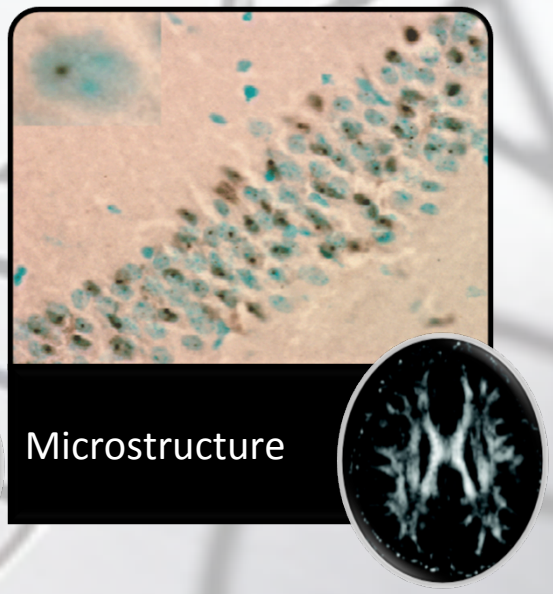


Rodriguez-Oroz, Lancet Neurology 2009

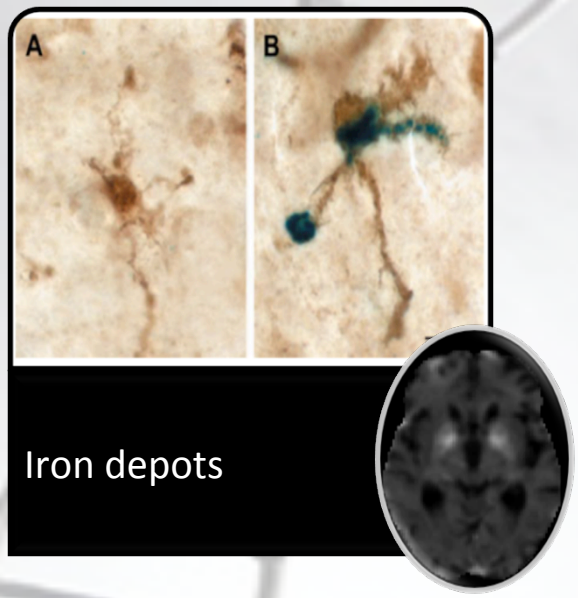
Imaging: biomarkers for therapeutic developpments in HD



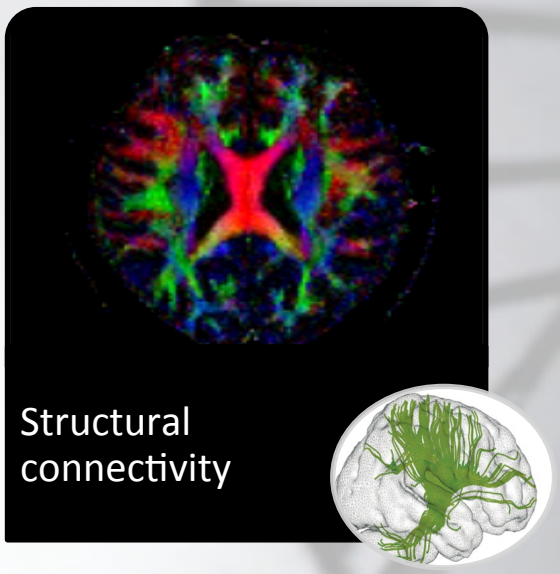
Brain volume



Microstructure

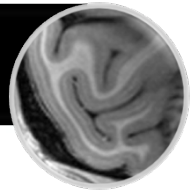


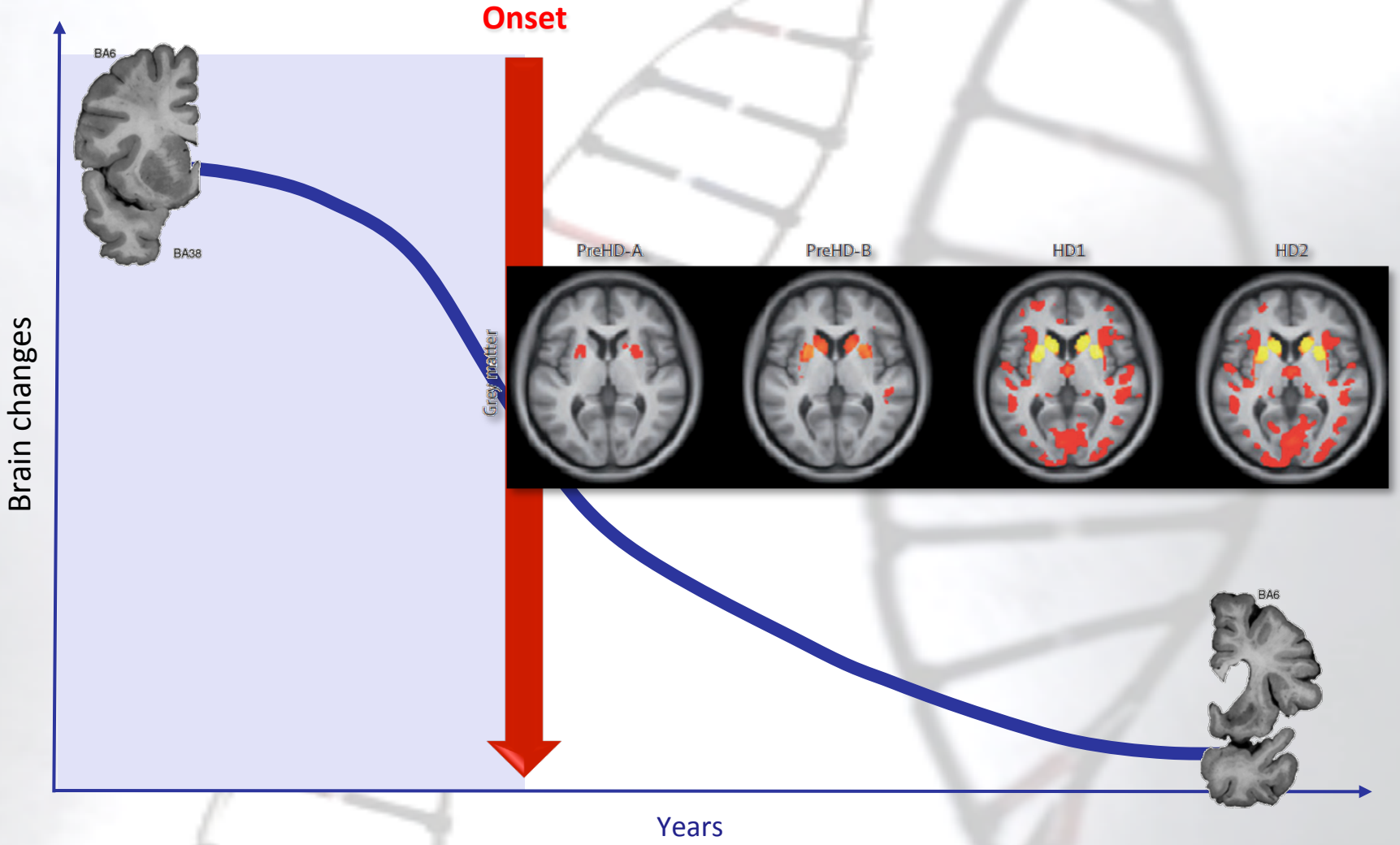
Iron depots



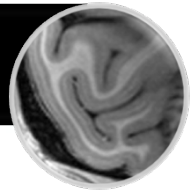
Structural connectivity

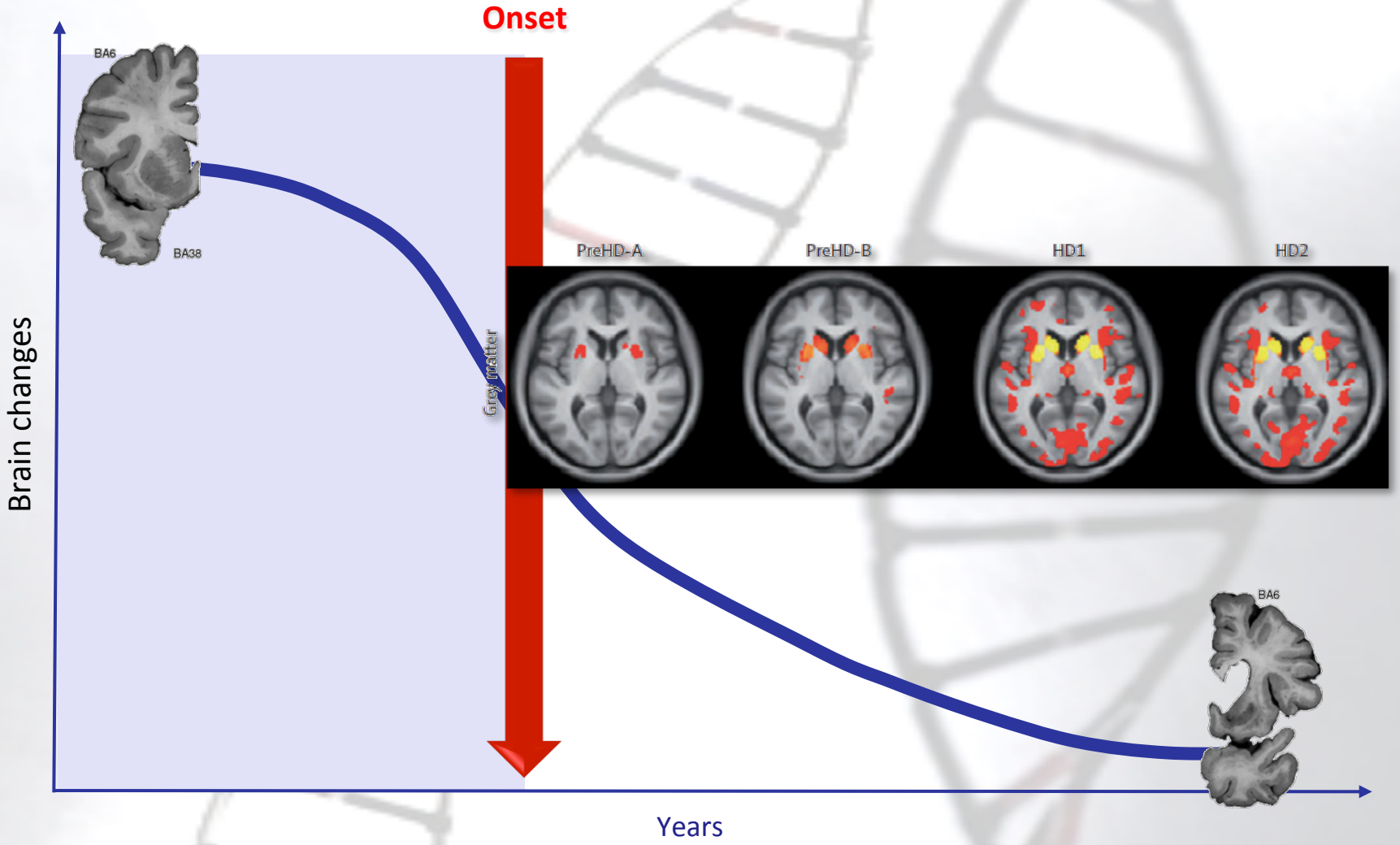
Brain volume



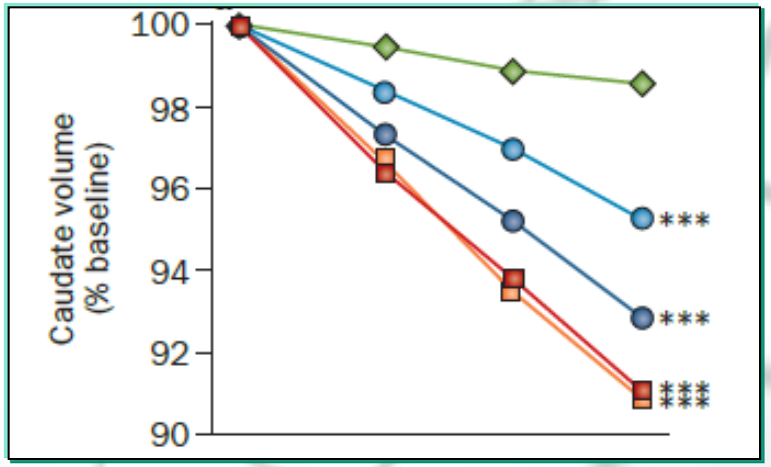


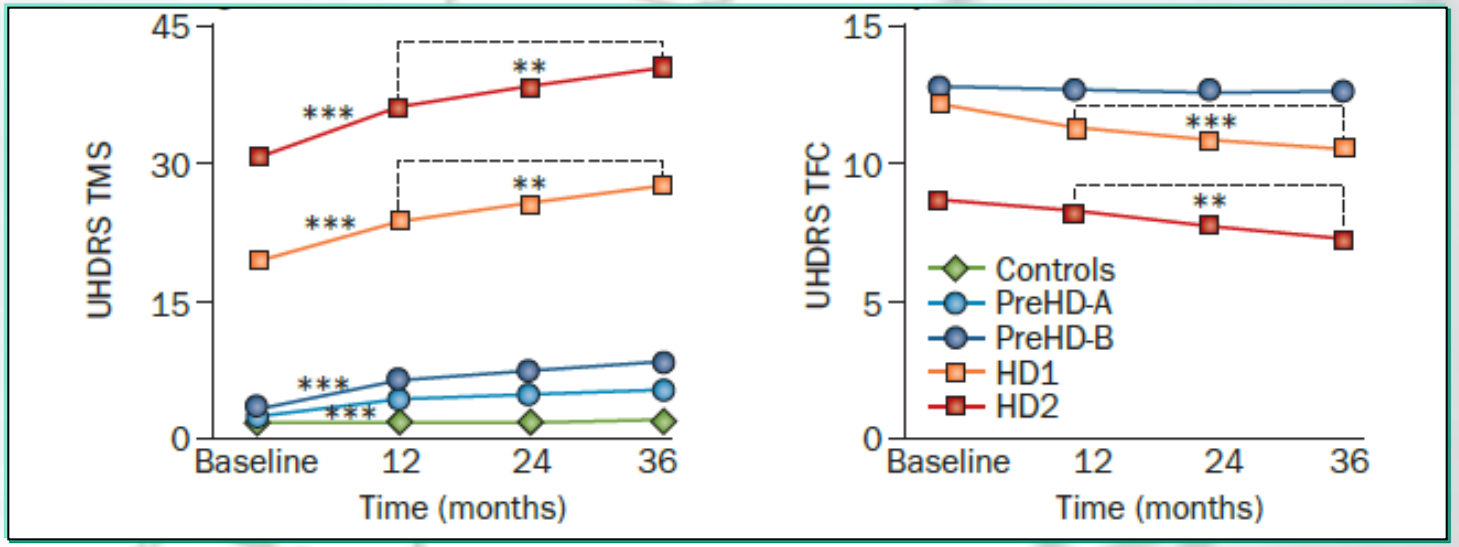
Brain volume





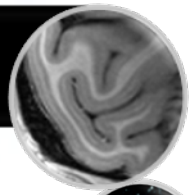
Longitudinal data from TRACK-HD



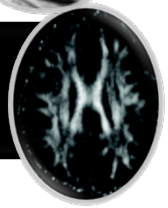


Tabrizi et al, The Lancet Neurology, 2013

Brain volume



Microstructure



Human Brain Mapping 34:1625–1635 (2013)

Seeking Huntington Disease Biomarkers by Multimodal, Cross-Sectional Basal Ganglia Imaging

Cristina Sánchez-Castañeda,[1,2] Andrea Cherubini,[1] Francesca Elifani,[3] Patrice Péran,[1,4] Sara Orobello,[3] Giovanni Capelli,[5] Umberto Sabatini,[1]* and Ferdinando Squitieri[3]*

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[2]Department of Psychiatry and Clinical Psychobiology, University of Barcelona, IDIBAPS, Barcelona, Spain
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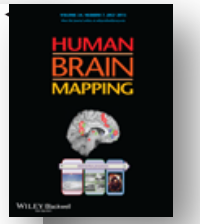
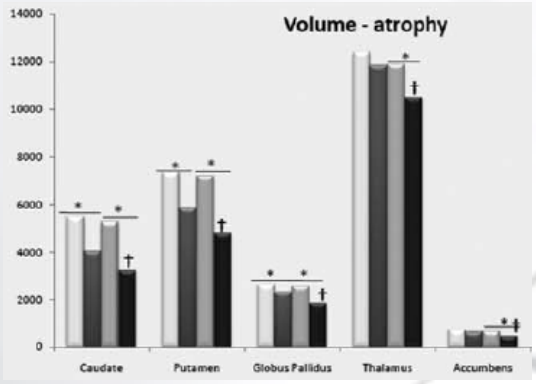
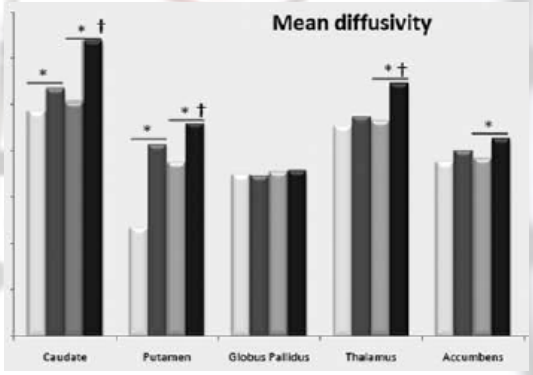
[4]INSERM U825, Université Paul-Sabatier, Toulouse, France
[5]Department of Health and Sport Sciences, University of Cassino, University of Cassino, Cassino, Italy

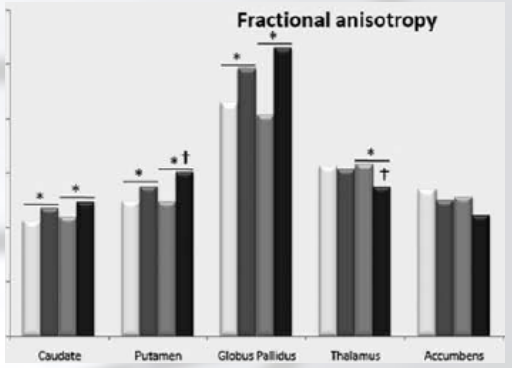


2013

Volume decrease and MD/FA increase in pre-HD and HD





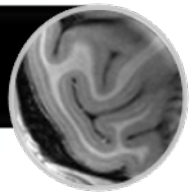


Volume = atrophy

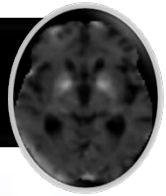
MD = reduced tissue integrity

FA = loss fiber integrity
increase astrocytes activity

Brain volume

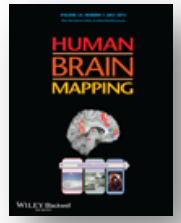


Iron depots



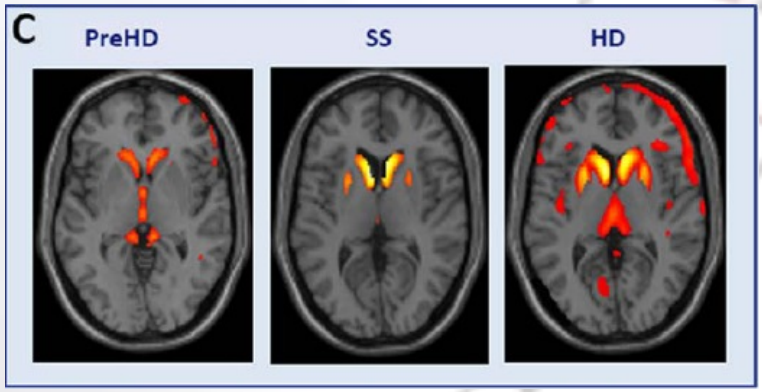
The Role of Iron in Gray Matter Degeneration in Huntington's Disease: A Magnetic Resonance Imaging Study

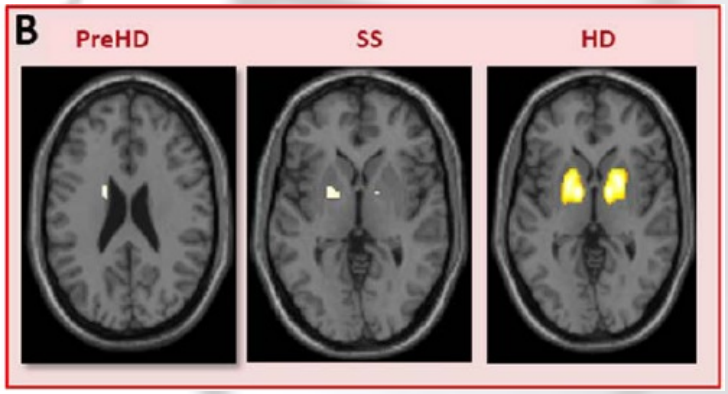
Cristina Sánchez-Castañeda,[1,2] Ferdinando Squitieri,[3] Margherita Di Paola,[1,4] Michael Dayan,[1] Martina Petrollini,[3] and Umberto Sabatini[1]



2014

Volume decrease and iron increase in pre-HD and HD

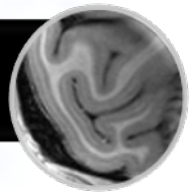




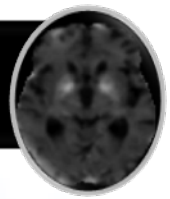
Volume = atrophy

Iron = increase of depots
neuro-degeneration

White matter volume



Iron depots



Multimodal MRI Analysis of the Corpus Callosum Reveals White Matter Differences in Presymptomatic and Early Huntington's Disease

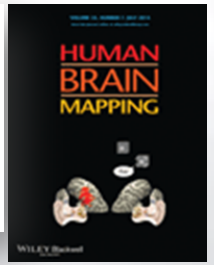
M. Di Paola[1,2], E. Luders[3], A. Cherubini[4,5], C. Sanchez-Castaneda[4,6], P. M. Thompson[3], A. W. Toga[3], C. Caltagirone[1,7], S. Orobello[8], F. Elifani[8], F. Squitieri[8] and U. Sabatini[4]

2012

MRI Measures of Corpus Callosum Iron and Myelin in Early Huntington's Disease

M. Di Paola,[1,2]* O. R. Phillips,[1] C. Sanchez-Castaneda,[3,4] A. Di Pardo,[5] V. Maglione,[5] C. Caltagirone,[1,6] U. Sabatini,[3] and F. Squitieri[5]

2013

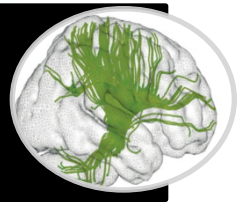


CC volume progressively decrease in pre-HD and HD

Demyelination occurs early, followed by axonal damage

Iron decrease later and differentiate Pre-HD from early HD

Structural connectivity



Tractography of the Corpus Callosum in Huntington's Disease

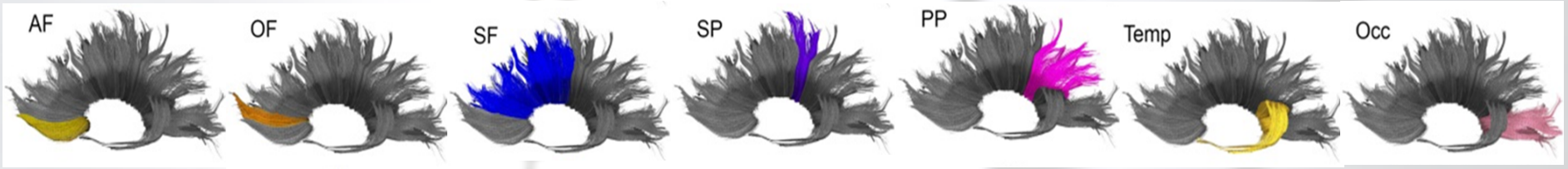
Owen Phillips[1], Cristina Sanchez-Castaneda[2], Francesca Elifani[3], Vittorio Maglione[3], Alba Di Pardo[3], Carlo Caltagirone[1,4], Ferdinando Squitieri[3], Umberto Sabatini[2], Margherita Di Paola[1,5]*

PLOS

2014

Structural connectivity impairments in pre-HD and HD

Impairments start in motor and visual tracts, proceed in P-A direction



Impairments is correlated with motor and cognitive scores (UHDRS1–2)

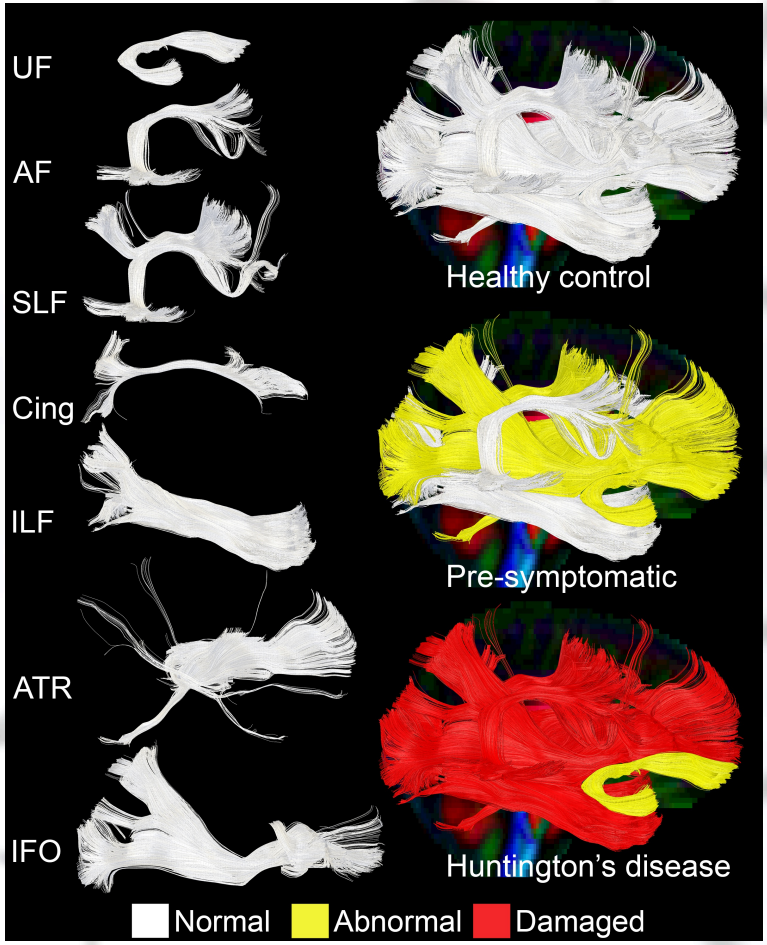
Deep White Matter in Huntington's Disease

Owen Phillips[1], Ferdinando Squitieri[2]*, Cristina Sanchez-Castaneda[3], Francesca Elifani[2]
Carlo Caltagirone[1,4], Umberto Sabatini[3], Margherita Di Paola[1]*

PLOS

2014

Individual Deep White Matter Tractography in HD



Individual WM tracts are impaired in specific manner in Pre-HD: spared ILF, partially damaged IFO, UF, AF, Cing, more damaged SLF and ATR

1 – Progressive grey and white matter alterations

2 – Dysfuntion and death

3 - Surviving neurons, new neurons recruited
(Cortical plasticity)

4 - Axonal sprouting, sinaptogenesis, pathways recruited
(Subcortical plasticity)

resiliency

Brain remapping
Changes in structure and function

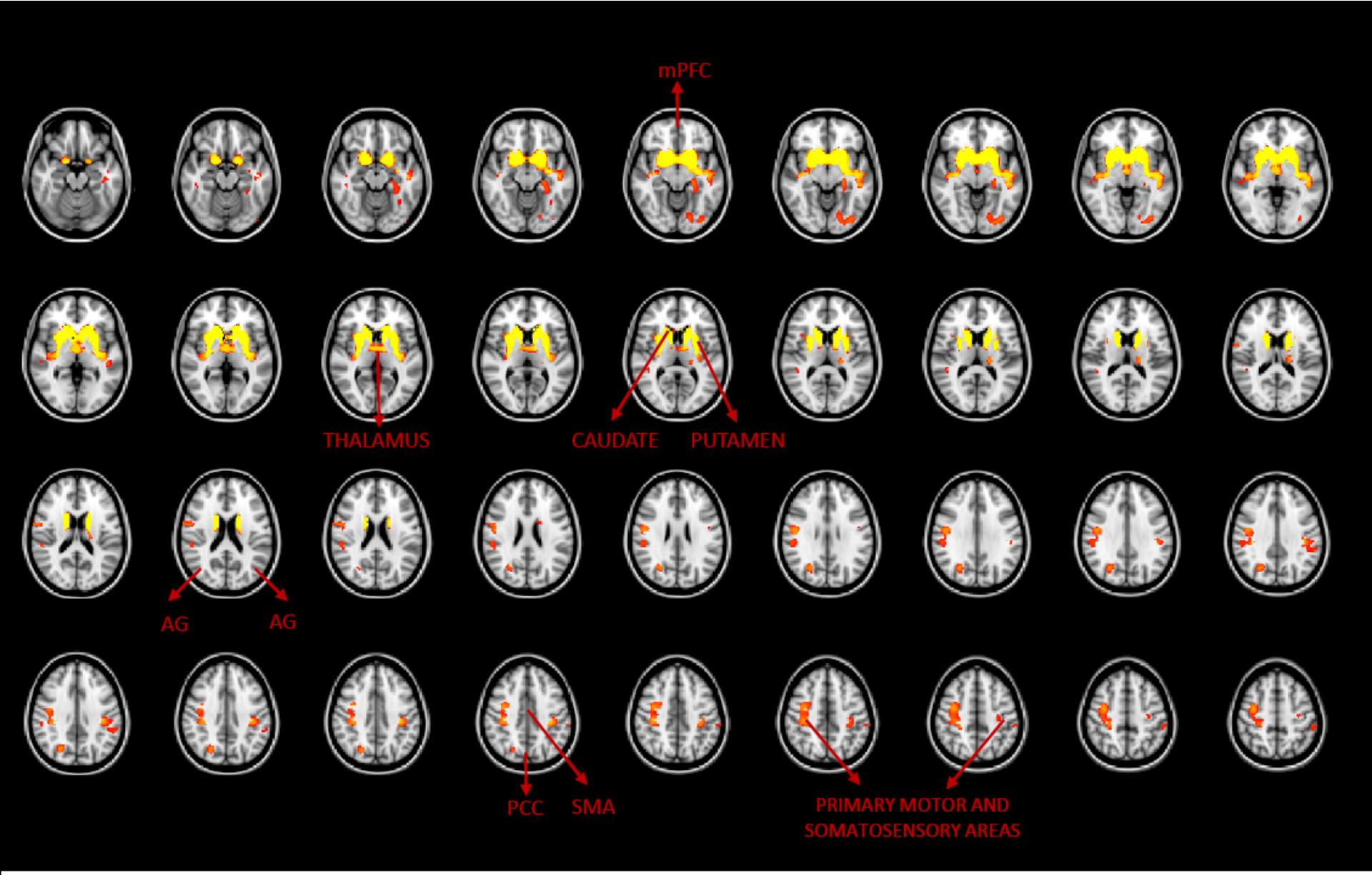


Figure 1. Areas of significant gray matter volume loss in Huntington's disease patients compared to controls (FWE corrected, *p < 0.05*). The indicated areas are the main components of the Motor and the Default Mode Networks.

Abbreviations: AG, angular gyrus; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; SMA, supplementary motor area

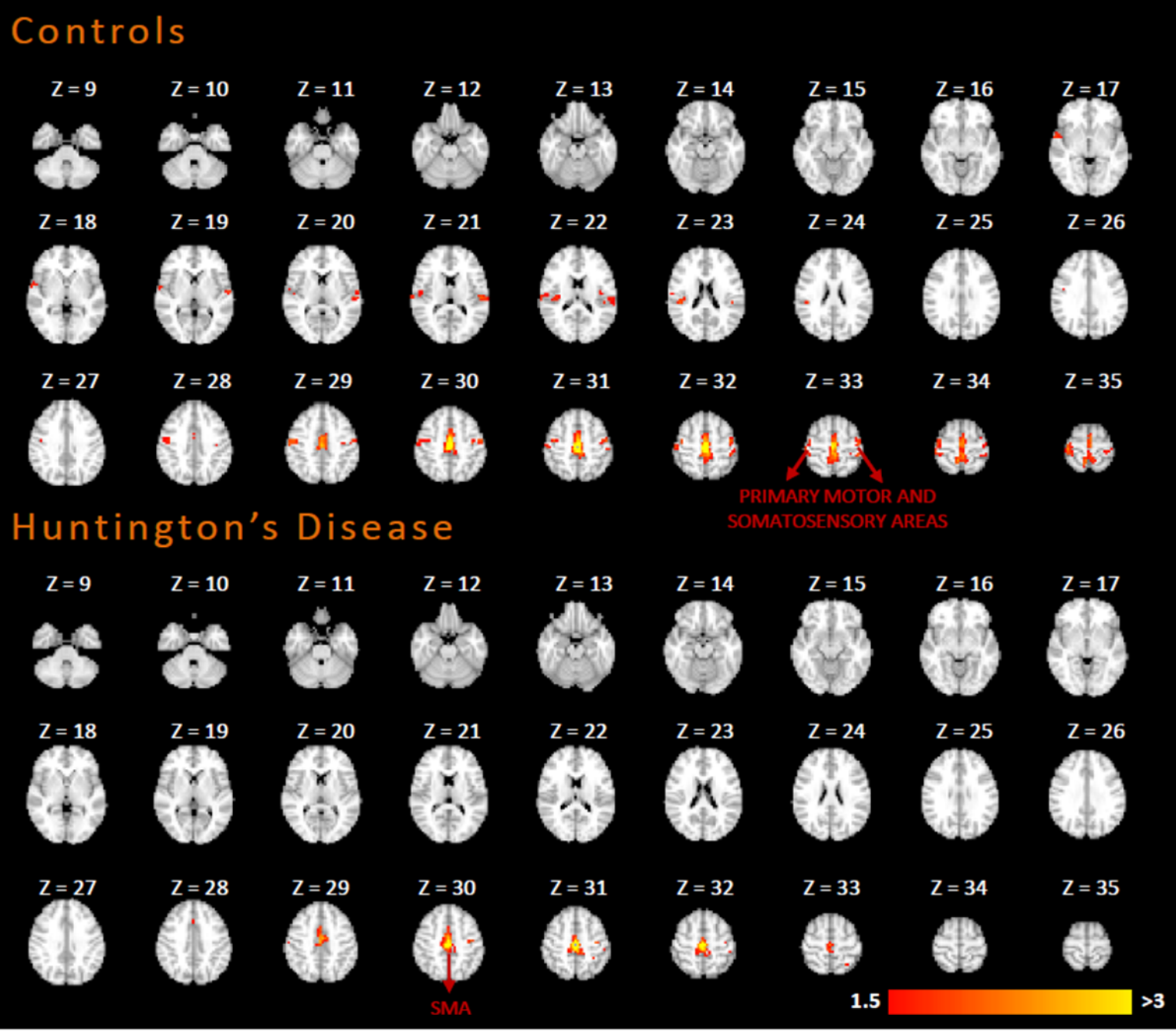


Figure 2. Average Motor network maps of the Huntington's disease and Control groups. The color bar indicates the Z values.

Conclusions

Take home messages: quantitative imaging

- Biomarker
- Structural and functional brain changes in HD
- Correlation with clinical scores
- Disease-modifying therapeutics

THANKS TO

PATIENTS AND FAMILIES WHO GIVE THEIR TIME TO ALL HD STUDIES